Application No. 09/252,691
Attorney's Docket No. 107196.135 (PATH99-03)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

#32
Linda
7-8-03

In re Patent Application of:

Keith G. Weinstock, Craig Deloughery, and David Bush

Application No.: 09/252,691

Filed: February 18, 1999

For: NUCLEIC ACID AND AMINO ACID SEQUENCES RELATING TO *ENTEROBACTER CLOACAE* FOR DIAGNOSTICS AND THERAPEUTICS

**BOX AF**

Group Art Unit: 1645

Examiner: Virginia Portner

Appeal No._____



CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Alexandria, VA 22313
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## BRIEF FOR APPELLANT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This appeal is from the decision of the Primary Examiner dated August 14, 2002 (Paper No. 26), finally rejecting claims 1-10, 29-41, 43-45, and 47-50, which are reproduced as an Appendix to this brief.

The Commissioner is hereby authorized to charge Deposit Account No. 501040 the $320.00 fee for filing a brief in support of an appeal. Two copies of this brief are being filed herewith.

A four-month extension of time from the Notice of Appeal to respond to the Final Office Action is respectfully requested. A Petition for a four-month extension of time is

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being filed concurrently. The Commissioner is hereby authorized to charge Deposit Account No. 501040 the $1450 for the Petition. Thus, the Commissioner is authorized to charge Deposit Account No. 501040 a total of $1770 for the Petition and Brief for Appellant.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 501040. This paper is submitted in triplicate.

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## I. INTRODUCTION

This is an appeal under 37 C.F.R. § 1.191 from the decision of the Examiner as set forth in the Official Action dated August 14, 2002 (*i.e.*, Paper No. 26). In response to the Official Action of August 14, 2002, which finally rejected claims 1-10, 29-41, 43-45, and 47-50, Appellants filed an After Final Amendment and Reply on April 25, 2003. During a personal communication with the Examiner on May 15, 2003, the Examiner indicated that the April 25, 2003 Amendment and Reply would not be entered upon filing an appeal and that claims 1-10, 29-41, 43-45, and 47-50 remain rejected.

Finally rejected claims 1-10, 29-41, 43-45, and 47-50 are attached hereto as Appendix A to this brief. A Notice of Appeal was filed November 12, 2002 and received in the U.S. PTO on November 15, 2002. Attached is a Petition for a four-month Extension of Time and corresponding fee, extending the period for response to May 15, 2003.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 501040. This paper is submitted in triplicate.

## II. REAL PARTY IN INTEREST

The present application is assigned to Genome Therapeutics Corporation.

## III. RELATED APPEALS AND INTERFERENCES

Neither the assignee nor their legal representatives know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

## IV. STATUS OF CLAIMS

This Application was filed on February 18, 1999 with 28 claims, 9 of which were independent. The filing date of February 18, 1999 was granted and priority under 119(e) was acknowledged.

On September 15, 1999, an Official Action (Paper No. 5) was mailed restricting the claims into nine groups. Via a Reply dated on January 19, 2000, Applicants elected Group I (*i.e.*, claims 1-13, drawn to isolated nucleic acid molecules, vectors, host cells, a method of using said host cells to produce a polypeptide, and vaccine compositions), along with 1 sequence for examination (*i.e.*, SEQ ID NO: 1394).

On July 13, 2000, an Official Action was mailed (Paper No. 14), rejecting claims 1-13. Claims 14-28 were withdrawn as directed to non-elected subject matter. On November 13, 2000, Applicants amended claims 1, 5, 9 and 10.

On February 22, 2001, an Official Action was mailed (Paper No. 19), rejecting claims 1-13. On June 22, 2001, Applicants amended claims 1, 5, 9-13 and added new claims 29-50.

On September 25, 2001, an Official Action was mailed (Paper No. 22), that allowed claims 42 and 46 and rejected claims 1-13, 29-41, 43-45, and 47-50. On March 25, 2002, Applicants amended claim 10 and canceled claims 11-13.

On August 14, 2002, an Official Action was mailed (Paper No. 26), which finally rejected claims 1-10, 29-41, 43-45, and 47-50. On April 25, 2003, Applicants submitted amendments to claims 1, 5, 9, 29, 33, 37, and 50 and canceled claim 10 in an Amendment After Final.

On May 15, 2003 the Examiner contacted Applicants' representative, advising Applicants that the amendments to claims 1, 5, 9, 29, 33, 37, and 50 were not entered and the cancellation of claim 10 was not entered.

On November 12, 2002, Appellant submitted a Notice of Appeal and today appeals the final rejection of claims 1-10, 29-41, 43-45, and 47-50.

The status of the claims is as follows:

| | |
|---|---|
| allowed claims: | 42 and 46 |
| claims objected to: | none |
| claims rejected: | 1-10, 29-41, 43-45, and 47-50 |
| claims canceled: | 11-28 |

## V. STATUS OF AMENDMENTS

The amendments to Claims 1, 5, 9, 29, 33, 37, and 50 and claim 10 canceled by Applicants on April 25, 2003 were not entered. Therefore, the pending claims are those as last examined by the Office and reflected in the Office Action dated August 14, 2002.

## VI. SUMMARY OF THE INVENTION

***Scientific Background of Enterobacter cloacae.***

Antibiotic resistance is a major problem in the control of infectious diseases. *Enterobacter cloacae* is a very serious pathogen of humans, multiplying quickly and resulting in the deaths of infected individuals, including children. There is an increased frequency of bacterial resistance in the Intensive Care Units of hospitals due partly to this organism. Strains of *E. cloacae* resistant to broad-spectrum penicillins and beta-lactamase-stable cephalosporins occurs at a frequency of $10^7$ to $10^6$.[1] Selected fluroquinolones have often been successfully administered to patients with urinary tract infections; however, *E. cloacae* has become resistant to many of them.[2] Some resistance has been attributed to plasmid-containing *E. cloacae* and some to the *E. cloacae* chromosome. In Holland, two different resistant strains of *E. cloacae* have been identified. The Amsterdam strain (resistant to ceffotaxin and piperacillin) exhibits depressed chromosomal Class 1 beta-lactamase, whereas the Rotterdam strain (resistant to cefuroxine) favors the spread of a plasmid encoding TEM-2 beta-lactamase.[3] Resistant strains of *E. cloacae* developed within 6 days in nearly 50% of the *E. cloacae*-infected intensive care patients with pulmonary complications treated with cefotaxime.[4] While several antimicrobial agents retain potent activity against the highly resistant organisms[5], constant exposure to these agents may eventually result in resistance.

***Summary of Claimed Invention.*** Applicants' invention is directed toward isolated nucleic acids and polypeptides derived from the human pathogen, *E. cloacae,* that are useful as

[1] Kadima, T.A. and Weiner,J.H., 1997, Antimicrobiol. Agents Chemother. 41:2177-2183; Lampe, M.F., et al, Antimicrob. Agents Chemother. 21:655-660; Lindberg, F., et al, Rev. Infect. Dis. 8 [Suppl 3]:S292-S304.

[2] Deguchi, T., et al, 1997, Antimicrobiol. Agents Chemother. 41: 2544-2546.

[3] Namavar, F., 1997, BIO 99-53 99-606615.

[4] Fussle, et al., 1994, Clin. Investig. 72:1015-1019.

[5] Pfaller, M.A., 1997, Diagn. Microbiol. Infect. Dis. 28:211-219.

targets for diagnosis and treatment of pathological conditions resulting from bacterial infections. Specifically, this invention is directed to an isolated nucleic acid comprising a nucleotide sequence encoding an *E. cloacae* polypeptide of SEQ ID NO: 1394, wherein SEQ ID NO:1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 1). The invention is further directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 2). The invention is further directed to a cell comprising the recombinant expression vector (claim 3). The invention is further directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide (claim 4).

Another aspect of the invention is directed to an isolated nucleic acid comprising at least 25 sequential bases of SEQ ID NO: 1394 encoding an *E. cloacae* polypeptide or fragment thereof, wherein SEQ ID NO:1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 5). The invention is further directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 6). The invention is further directed to a cell comprising the recombinant expression vector (claim 7). The invention is further directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide (claim 8).

The invention is further directed to a probe comprising a nucleotide sequence including at least 25 sequential nucleotides of SEQ ID NO: 1394, wherein SEQ ID NO:1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 9).

Another aspect of the invention includes an isolated nucleic acid comprising a nucleotide sequence of at least 30 consecutive nucleotides in length, wherein the sequence can hybridize under conditions of high stringency to a nucleic acid comprising SEQ ID NO:1394, wherein said nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 10).

The invention is further directed to an isolated nucleic acid of SEQ ID NO: 7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 29), a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 30), and a cell comprising the recombinant expression vector (claim 31). The invention is also directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide (claim 32).

The invention is further directed to an isolated nucleic acid that encodes a polypeptide of *E. cloacae* consisting of a range of residues which is 3-222, 6-222, or 13-222 of SEQ ID NO:7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 33). The invention is also directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 34), a cell comprising the recombinant expression vector, wherein the cell expresses the polypeptide encoded by SEQ ID NO: 1394 (claim 35), and a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide encoded by SEQ ID NO:1394 (claim 36).

Another aspect of the invention is directed to an isolated nucleic acid encoding a polypeptide which comprises at least 90% sequence identity with SEQ ID NO:7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 37). The invention is also directed to the isolated nucleic acid, wherein the polypeptide comprises at least 95% sequence identity with SEQ ID NO: 7056 (claim 38). The invention is also directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 39). The invention is also directed to a cell comprising the recombinant expression vector (claim 40). The invention is also directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide (claim 41).

Another aspect of the invention is directed to an isolated nucleic acid consisting of SEQ ID NO:1394 (claim 42). The invention is also directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 43). The invention is also directed to a cell comprising the recombinant expression vector, wherein the cell expresses the polypeptide encoded by SEQ ID NO:1394 (claim 44). The invention is also directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide (claim 45).

The invention is further directed to an isolated nucleic acid consisting of nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO:1394 (claim 46). The invention is also directed to a recombinant expression vector comprising the isolated nucleic acid operably linked to a transcription regulatory element (claim 47). The invention is also directed to a cell comprising the recombinant expression vector, wherein the cell expresses the polypeptide encoded by nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO:1394 (claim 48). The invention is also directed to a method for producing an *E. cloacae* polypeptide comprising culturing the cell under conditions that permit expression of the polypeptide encoded by nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO:1394 (claim 49).

Another aspect of the invention is directed to a probe comprising a nucleotide sequence including at least 30 sequential nucleotides of SEQ ID NO:1394, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which SEQ ID NO:1394 is immediately contiguous in the naturally occurring *E. cloacae* genome (claim 50).

Support for the invention can be found at least in the parent applications, U.S. Provisional Application No. 60/074,787, filed on January 29, 1999 and U.S. Provisional Application No. 60/094,145 filed July 24, 1998. Support for the invention may be found, at least, in the specification, especially on page 10, line 4 to page 12, line 7 (*E. cloacae* polypeptides and amino acid sequences, and discussion of sequence identity), page 13, lines 3-10 (a nucleic acid encoding an *E. cloacae* polypeptide which can hybridize under stringent conditions to a probe), page 14, line 3 to page 19, line 4 (isolated nucleic acids of the present invention), page 23, line 23 to page 24, line 3 (*E. cloacae* biological activity), page 30, line 5 to page 32, line 15 (*E. cloacae* genomic sequences), pages 37-47 (expression of *E. cloacae* sequences) and pages 47-48

(identification and use of *E. cloacae* sequences), Table 2 (open reading frames (ORFs) of reference sequences), the Sequence Listing, and in the claims as originally filed.

## VII. THE ISSUES

1. Whether claims 1-10, 29-41, 43-45, and 47-50 lack utility and whether the Specification teaches one skilled in the art how to use the claimed invention?

2. Whether the Specification provides written description support and an enabling disclosure for claims 29, 33, 37-38?

3. Whether Claims 5, 9, 29, and 50 are anticipated by Blattner *et al.* or Oshima *et al.*?

## VIII. GROUPING OF CLAIMS

1. For the purposes of the rejection of claims 1-10, 29-41, 43-45, and 47-50 under 35 U.S.C. § 101 and § 112, first paragraph, these claims stand or fall together.

2. For the purposes of the rejection of claims 29, 33, 37-38 under 35 U.S.C. § 112, first paragraph, for lack of written description support and enabling disclosure, these claims stand or fall together.

3. For the purposes of the rejection of claims 5, 9, 29, and 50 under 35 U.S.C. § 102(b) as allegedly anticipated by Blattner *et al.* or Oshima *et al.*, these claims stand or fall together.

## IX. ARGUMENT

### *1. The rejection of Claims 1-10, 29-41, 43-45, and 47-50 under 35 U.S.C. § 101 and § 112, first paragraph*

The Official Action dated August 14, 2002 (Paper No. 26), finally rejects claims 1-10, 29-41, 43-45, and 47-50 under 35 U.S.C. § 101 and § 112, first paragraph. The rejection under § 112, first paragraph will stand or fall with the rejection under § 101. The additional rejections under 35 U.S.C. § 112, first paragraph are to be construed separately as to each claim and from these rejections. Accordingly, Applicants mainly will address the § 101 requirement below.

The Examiner has rejected claims 1-10, 29-41, 43-45, and 47-50 under 35 U.S.C. §101 because the claimed invention is not supported by a specific, credible, and substantial utility or a well-established utility for the elected invention. See August 12, 2002 Office Action.

Applicants submit that the Examiner is in error.

To establish a *prima facie* case for lack of utility the Examiner must show by a preponderance of evidence that it is more likely than not that the asserted utility would be considered false by a person of ordinary skill. M.P.E.P. § 2107.01 and *In re Corkill*, 226 U.S.P.Q. 1005, 1008 (Fed. Cir. 1985). Applicants submit that the Examiner has not demonstrated that it is more likely than not that all of the asserted utilities would be considered false by a person of ordinary skill.

The USPTO itself has recognized that the burden of showing a lack of utility under 35 U.S.C. § 101 is significant in the M.P.E.P. at § 2107.02(III)(B), which cautions the Examiner that rejections under 35 U.S.C. § 101 have rarely been sustained by the federal courts. Generally speaking, in these rare cases, the applicant either failed to disclose any utility of the invention or asserted an utility that could only be true if it violated scientific principle . . . or was wholly inconsistent with contemporary knowledge in the art. *See In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967). The Federal Circuit has determined that to sustain a rejection under 35 U.S.C. § 101, the claimed invention "must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992) (emphasis added). *See also, E.I. du Pont de Nemours & Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 U.S.P.Q. 1, 10 n.17 (8th Cir. 1980).

Applicants argue herein that the Examiner has not met her burden. Moreover, even if the Examiner has met her burden, Applicants will discuss herein, that the invention does meet the utility requirement under 35 U.S.C. § 101.

Applicants assert that a well-established utility and a specific, substantial, and credible utility have been established for the claimed invention. At a minimum, the elected sequence, isolated from a highly-infectious human pathogen, and the compositions of the present invention may be used as probes for diagnostic assays, molecular targets for identification of new antimicrobials agents, and targets for vaccine development. See Exhibits 1, 2, and 3.

The Manual of Patent Examining Procedure (MPEP) states at § 2107.01, that research tools can be "useful" in a patent sense:

> Many research tools such as . . . nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

Therefore, nucleotide sequencing techniques, which can include microbial genomic databases containing nucleic acid sequences, amino acid sequences and sequence homology information of bacterial genes that are, in turn, useful in the functional analysis of the bacterial genome, can meet the utility requirement of 35 U.S.C.§ 101 if, for example, the nucleic acid sequences and proteins encoded by the nucleic acid sequences have a well-established utility or, in the alternative, a specific, substantial, and credible utility such as in the development of antibiotics, diagnostics, vaccines, and drugs to treat humans afflicted with infection caused by the bacteria.

**A. The Specification Asserts A Well-Established Utility For The Claimed Invention**

The MPEP states, at § 2107.02B, that the utility of 35 U.S.C. § 101 is met, even if a specific, substantial, and credible utility for the claimed invention is not asserted in the Specification, if such utility is well-established:

> An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

The guidelines for examination of patent applications under 35 U.S.C. § 101, "utility" requirement referenced by the Examiner, as shown in the Federal Register, Vol. 66, No. 4, pages 1092-1099, at page 1095, states:

> By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit.

The Federal Register, Vol. 66, No. 4, page 1097 also states:

> Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an [A]pplicant may rely on any one of those utilities without prejudice. (emphasis added).

The invention involves nucleic acid and amino acid sequences relating to *Enterobacter cloacae*. Many sources written by those skilled in the biological sciences describe the utility of sequence information from microbial pathogens as well-established in the art. For example, as shown in Exhibit 1, Moir, D.T., *et al., Antimicrob. Agents Chemother. 43:* 439-446 (1999), states, on page 439, that genomic sequence information has provided a wealth of information useful to assist in the development of strategies for antimicrobial drug discovery:

> [H]igh-throughput automated random genomic DNA sequencing together with robust fragment assembly tools has delivered a wealth of genomic sequence information to assist in the search for new targets. In many cases, entire biochemical pathways can be reconstructed and compared in different pathogens.

Further, Moir *et al.,* states, on page 440-441, that essential genomic sequence information is useful in identifying potential targets for new antimicrobials:

> Genes which are essential to pathogenesis and prevent colony formation in a conditional-lethal manner are potential targets for new antimicrobials.

In addition, Tatusov, R.L., *et al., Science 278:* 631-637 (1997), Exhibit 2, on page 631, states that comparisons of complete genomic sequences of bacteria are useful and can be critically important to the development of targets for new antibiotics:

> With multiple genome sequences, it is possible to delineate protein families that are highly conserved in one domain of life but are missing in the others. Such information may be critically important: For example, the families that are conserved among bacteria but are missing in eukaryotes comprise the pool of potential targets for broad-spectrum antibiotics.

Smith, D.R., *TIBTECH 14*: 290-293(1996), Exhibit 3, states, on pages 291-292, that the first task in identifying new strategies for therapeutics and vaccine targets is to identify genes of the

microbial organism and that the second task is identifying sequence homology which is useful in the analysis of gene products. Specifically, Smith states on page 292:

> The second phase in the analysis of bacterial genomes is to identify the function of as many genes as possible. Currently, sequence homology is the most powerful tool. A high degree of homology between the putative translation product of a newly identified gene and an enzyme whose function has been thoroughly studied in other organisms, provides strong support for the function of that protein.

In addition, Smith states, on page 293, that microbial genome sequence information is useful in new strategies for identifying drug or vaccine development targets by targeting essential genes:

> The techniques described in the previous section can be used to identify genes in specific functional categories that may represent good targets for drug or vaccine development. In general, when developing new antibiotics, one is interested in genes that are essential under all growth conditions . . . .

Furthermore, the Specification discusses additional well-established utilities of the *E. cloacae* nucleotide sequences. For example, the nucleotide sequences can be useful for developing probes used in diagnostics to detect the presence of the *E. cloacae* pathogen, more rapidly and accurately than is now possible, thus allowing earlier intervention in life-threatening infections such as *E. cloacae* sepsis. See Specification, page 34, line 15 to page 35, line 6. The nucleotide sequences can be useful for creating primers to amplify *E. cloacae* nucleic acids sequences. See Specification, page 35, line 23 to page 36, line 17. The nucleotide sequences are useful for the creation of antisense agents, which can be used to prevent the expression of *E. cloacae* genes. See Specification, page 36, line 19 to page 37, line 12.

The usefulness of the claimed invention includes providing information to assist in new drug discoveries, assisting in the development of targets for new antibiotics, and identifying new drug or vaccine development targets. The claimed invention can also be used as a means of diagnosing a patient or a biological sample with *E. cloacae*. These uses are apparent and implied by the Specification when taken with knowledge of one skilled in the art at the time of Applicants' invention. The claimed invention has a well-established utility. Thus, Applicants respectfully submit that the Examiner is incorrect in applying the rejection under 35 U.S.C. § 101.

**B. The Specification Asserts A Credible, Specific, And Substantial Utility For The Claimed Invention**

1. The claimed sequences have a specific utility.

The MPEP states at § 2107.01 that a specific utility is:

> A "specific utility" is specific to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of invention. . . . [T]he situation where an [A]pplicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the . . . category are sufficient to identify a specific utility for the invention.

Applicants have shown that Table 2 of the Specification contains the nucleotide SEQ ID in the first column along with the corresponding protein in the second column. For example, the nucleotide sequence in SEQ ID NO:1394 encodes the amino acid sequence in SEQ ID NO:7056.

Moreover, Applicants have presented to the Examiner results from sequence alignments for the amino acid sequences encoded by the nucleotide sequences of the presently claimed invention. These alignments refer to the reference sequences provided in Table 2 of the Specification. The summary table provides the claimed nucleotide SEQ ID NO., the corresponding amino acid SEQ ID NO., reference sequence, reference gene name, and the percent identity. In addition to the summary table below, the sequence alignment itself is submitted as Exhibit 4 to visually reinforce that the claimed sequences are homologs of the reference sequences. These results were produced using the GCG Best Fit algorithm, which makes an optimal alignment between segments of sequences based on similarity.

Summary Table of Sequence Alignments and
Table 2 of Specification

| Claimed Nucleotide SEQ ID NO: | Corresponding Amino Acid SEQ ID NO: | Reference Sequence | Reference Gene Name | % identity |
|---|---|---|---|---|
| 1394 | 7056 | B1135 | ymfc | 85.0 |

The sequence alignment shows that there is a high degree of identity and similarity between the claimed sequences and the reference sequences from Table 2 of the Specification. By way of explanation of sequence alignment accuracy, Applicants submit the reference (Exhibit 5) by Rost, PROTEIN ENGINEERING, 12:85-94 (1999). Rost discloses that the accuracy of the results of sequence alignments is much higher when the sequence identity percentage is greater than 35%, because the number of false positives is drastically reduced at this point. Thus, to those of skill in the art, a sequence identity higher than 35% is an accurate result. See Rost, pages 91-92.

Applicants note that the alignment of the claimed sequence yield a sequence identity percentage much higher than the threshold of 35%. The sequence identity is 85%. Applicants point to the paragraph at the bottom of the first column of page 92 of the Rost publication, wherein Rost states that "[f]rom 100-35% sequence identity, any residue exchange resulting in a stable structure maintains structure."

The Examiner also states that:

> [T]he primary structure of a putative polypeptide does not define the nucleic acid that encodes the polypeptide as a specific diagnostic agent and the polypeptide is not defined to have any specific function, just a putative structure.

The Examiner has taken the position that the functional identification of polypeptide SEQ ID NO:7056 encoded by SEQ ID NO:1394 in Table 2 of the Specification is identified at page 53, line 7 as "putative." The definition of putative is (1) commonly accepted or supposed, (2) assumed to exist or have existed (See, for example, Merriam-Webster Collegiate Dictionary Online http://www.m-w.com/home.htm). Therefore, unless presented with a reason to doubt the identification, it should be taken as commonly accepted. The applicable standard is a credible utility and not a proven or certain utility. See, Utility Examination Guidelines, 66 FR 1092 (Jan. 5, 2001). The training manuals describe how this standard is to be applied as follows:

> Office personnel must determine if the assertion of utility is credible (*i.e.*, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). As assertion is credible unless (A) the logic underlying the assertion is

> seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. See the Revised Interim Utility Guidelines Training Materials of the U.S.P.T.O. at page 5.

The Examiner has not shown that either the logic underlying Applicant's assertion of utility is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

The Examiner further states that "[h]omology with other known polypeptides or nucleic acids does not define a nucleic acid as a specific diagnostic reagent, nor does it establish that polypeptide's specific function." The Examiner requests Applicant to point to the section of the instant Specification that defines the claimed nucleic acid to encode a polypeptide with pseudouridine synthase biological activity. Applicants have. By providing these search results, the specific function of the claimed nucleic acid is disclosed. To one of skill in the art, the claimed nucleic acid encodes a polypeptide with pseudouridine synthase activity.

Nucleic acid sequences and their encoded amino acid sequences, which are homologous to known sequences with accepted utility, can meet the utility requirement of 35 U.S.C. § 101, if, for example, the homologous nucleic acid and amino acid sequences have accepted utility and the nucleic acid and amino acids sequences of the invention assert a specific, substantial and credible utility, such as the function of the homologous protein. As stated in the Federal Register at Vol. 66, No. 4, at page 1096:

> More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the [E]xaminer unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." (citations omitted).

The claimed sequences of this invention meet this requirement as shown in the above table and discussed below.

SEQ ID NO:1394, which codes for SEQ ID NO:7056, encodes a homolog to *E. coli* pseudouridine synthase. Applicants would like to reference Koonin, submitted with Applicants'

Amendment and Reply of June 22, 2001, Koonin, Nucleic Acids Res. 24(12):2411-5 (1996), which discloses that:

> [I]t is shown that the four recently described pseudouridine syntheses with different specificities belong to four distinct families. Three of these families share two conserved motifs that are likely to be directly involved in catalysis. One of these motifs is detected also in two other families of enzymes that specifically bind uridine, namely deoxycitidine triphosphate deaminases and deoxyuridine triphosphatases. It is proposes that this motif is an essential part of the iridine-binding site. Two of the pseudouridine synthase, one of which modifies the anticodon arm of tRNAs and the other is predicted to modify a portion of the large ribosomal subunit RNA belonging to the peptidyltransferase center, are encoded in all extensively sequenced genomes, including the 'minimal' genome of Mycoplasma genitalium. These particular RNA modifications and the respective enzymes are likely to be **essential** for the functioning of any cell. (emphasis added)

Pseudouridine synthase is essential to the functioning of the cell. The high homology of Applicant's claimed sequence to pseudouridine synthase is a result of the maintenance of the conserved motifs of pseudouridine synthases and points to its essentiality in the cell. The disclosed sequences and the identification of this function meet the Utility Guidelines of the Federal Register; therefore, the Examiner must accept the asserted utility.

The Examiner states that "Koonin et al does not mention anything about *E. cloacae* whatsoever in the reference. One of skill in the art would not have ascertained that the *E. cloacae* nucleic acid that encodes pseudouridine synthase biological activity was known in light of the disclosure provided by Koonin et al."

One of skill in the art at the priority date of the present application would envision that the pseudouridine synthases taught by Koonin *et al.* has the same function across bacterial species including *E. cloacae* because of the sequence identity and conserved signature motifs. (Nucleic Acids Research, 24:2411-15, (1996)). Koonin teaches that pseudouridine synthases across bacterial genomes have certain signature motifs beyond the PROSITE motif. All three signature motifs taught by Koonin are found in the polypeptide SEQ ID NO:7056 encoded by SEQ ID NO:1394 as shown on page 11 of Applicants' Amendment and Reply of June 22, 2001. The teachings of Koonin present motifs which complement and expand on the PROSITE entries. Koonin also teaches that pseudouridine synthases perform essential functions. Koonin teaches

both the means of identification and the essential nature of the presently elected sequences of the invention.

The Examiner states that:

> The specific accession number P75966 was created November 1, 1997, but the comment section appears to be dated November 23, 1998 and defines the hypothetical protein to be a member of the pseudouridine synthase family. The description was provided to the public about *ymfc* after the filing date of the instant specification.

Applicants note that the Examiner has mistakenly interpreted the comment of the NCBI entry to indicate that the functional identification is dated November 23, 1998. However, this comment only indicates that entry gi:2501525 was replaced with a newer entry gi:3916025 on that date. The Koonin reference submitted by Applicants is the prior entry apparently dating from November 1, 1997. An unidentified portion of the annotation may have been updated on July 15, 1998. However, both the creation of entry gi:2501525 and the unidentified update precedes the filing date of the present application. Furthermore, Applicants wish to point out that Reference Sequence B1135 listed in Table 2 was already in the public domain at the time of the filing of the application. By reference to public databases known to and routinely used by one of skill in the art, one would have appreciated that this information identifies the polypeptide product as pseudouridine synthase of the RsuA family. For example, SWISSPROT entry accession No. P75966 (NCBI entry PID gi:2501525 and gi:3916025) was created November 1, 1997 prior to the filing of the application.

Applicants' claimed invention provides nucleic acid sequences that encode polypeptides used in diagnostics and therapeutics. Specifically, Applicants' claimed invention includes a wide variety of nucleic acid sequences which encode proteins that share homology with known proteins that have utility, several of which have been shown to be essential to the life of cell. Thus, Applicants submit that the claimed invention has a specific utility contrary to the Examiner's unsupported assertions.

2. The claimed sequences have a substantial utility.

The MPEP states at § 2107.01 that a substantial utility is defined as a utility that "defines a 'real world' use." For example, "a therapeutic method of treating a known or newly discovered disease . . . that themselves have a 'substantial utility' define a 'real world' context of use." *Id.* Given the important applications described in Moir *et al.*, Tatusov *et al.*, and Smith, Applicants submit that the development of diagnostics and treatments for life-threatening bacterial infections constitute a "real world" use. Therefore, the presently claimed invention provides a satisfactory substantial utility.

3. The claimed sequences have a credible utility.

Regarding credible utility, according to the MPEP at § 2107.01, "in view of the rare nature of such cases, Office personnel should not label an asserted utility 'incredible,' 'speculative' or otherwise unless it is clear that a rejection based on 'lack of utility' is proper." A credible utility is "assessed from the perspective of one of ordinary skill in the art, in view of the disclosure and any other evidence of record that is probative of the [A]pplicants assertions." Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001). The claimed sequences can be used as probes, capture ligands, primers, antisense agents, or diagnostic markers for the detection of specific disease causing pathogens. See Specification, page 34, line 15 to page 37, line 12. The relationship of the claimed nucleic acid sequences and corresponding amino acid sequences to essential, genes of other pathogens with clearly, defined functions and usefulness demonstrate that an Examiner would have no reason to dismiss the asserted utility as incredible or speculative. Thus, the claimed invention has a credible utility.

4. Conclusion

The Examiner has failed to meet her burden in showing by a preponderance of evidence that it is more likely than not that the asserted utility would be considered false by a person of ordinary skill. In addition, the claimed invention has a well-established and a specific, substantial, and credible utility, the claimed invention meets the requirements of 35 U.S.C. § 101. Accordingly, withdrawal of the rejection under 35 U.S.C. §101 is in order.

**C. Inconsistencies with the U.S. Patent and Trademark Office's application of 35 U.S.C. § 101**

There are inconsistencies in the treatment of Applicants' own patent estate specifically its pathogen portfolio. Applicants have filed related applications with the U.S. Patent and Trademark Office that differ from the present invention because they are related to pathogens other than *E. cloacae*. However, except for the difference in pathogen, the claimed subject matter is similar. The USPTO has examined these applications and issued three of them to date. For example, Applicants filed U.S. Patent Application No. 09/134,001 on August 13, 1998, which issued as U.S. Patent No. 6,380,370 ('370 patent) on April 30, 2002. In this application, the claims were directed to isolated nucleic acids that encode *Staphylococcus epidermidis* polypeptides. However, no rejections under 35 U.S.C. § 101 were ever brought to bear against the claims of the '370 patent during the course of prosecution, despite the fact that the claims were very similar to those of the present application. In addition, Applicants have also been issued U.S. Patent Nos. 6,562,958 relating to *Acinetobacter baumannii* and 6,551,795 relating to *Pseudomonas aeruginosa* from the same pathogen portfolio. These examples demonstrate the inconsistencies within the USPTO in interpreting the utility requirement. In the present case, the utility rejection is being improperly asserted by the Examiner, unlike in the '370 patent, where the utility issue was never even raised by the Examiner.

Moreover, there are inconsistencies in interpreting the utility requirement even within the present application. For example, the Examiner has allowed claims 42 and 46 but not

allowed the remaining claims. The question arises, how can the claims 42 and 46 directed toward nucleic acid sequence of SEQ ID NO:1394 be allowed and not the other claims which are also directed toward SEQ ID NO:1394. The Examiner has clearly misapplied the utility requirement in the present case.

**D. Rejection of Claims 1-10, 29-41, 43-45, and 47-50 Under 35 U.S.C. § 112, first paragraph**

Claims 1-10, 29-41, 43-45, and 47-50 are rejected under U.S.C. § 112, First Paragraph, since the claimed invention is not supported by either a specific, credible, and substantial utility or a well-established utility.

Applicants' argument *supra* demonstrates that the claimed invention is supported by a specific, credible, and substantial utility and a well-established utility. Accordingly, Applicants respectfully request the removal of the U.S.C. § 112, First Paragraph rejection.

***2. The Rejection of Claims 29, 33, and 37-38 under 35 U.S.C. § 112, first paragraph for lack of Enablement***

The Examiner has rejected claims 29, 33, and 37-38 under 35 U.S.C. § 112, first paragraph.

The Examiner states that:

> [T]he specification does not reasonably provide enablement for the use of any nucleic acid that only shares 70% sequence identity with SEQ ID NO:1394, based upon nucleic acid changes encompassed by claiming the isolated nucleic acid sequences by SEQ ID NO:7056.

Applicants assert that the Examiner is incorrect in her application 35 U.S.C. § 112, first paragraph. As stated on page 1102 of the Federal Register, Vol. 66, No. 4, disclosure of a single species can provide an adequate written description of a generic claim, if one skilled in the art would recognize that the disclosure of the species includes the genus:

> The Guidelines now indicate that a single species may, in some instances, provide an adequate written description of a generic claim when the

> description of the species would evidence to one of ordinary skill in the art that the invention includes the genus.

A disclosure "is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz,* 124 U.S.P.Q. 449, 502 (C.C.P.A. 1960). The rejection fails to set forth a *prima facie* case of non-enablement that is well-grounded in scientific reasoning or specific evidence as to why the full scope of the claims is not enabled. (M.P.E.P. § 2164.04).

The Specification as filed provides ample support for the Claims. For example, support for Claims 29, and 33 can be found on page 43 of the Specification, which states that:

> [D]ue to the degeneracy of the genetic code, many different nucleotide sequences can encode polypeptides having the amino acid sequences defined by SEQ ID NO: 5663 - SEQ ID NO: 11324 or sub-sequences thereof. The codons can be selected for optimal expression in prokaryotic or eukaryotic systems. Such degenerate variants are also encompassed by this invention.

Support for Claims 37, and 38 can be found on page 10 of the Specification, which states that:

> [T]he polypeptide has an amino acid sequence at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% identical to an amino acid sequence of the invention contained in the Sequence Listing[.]

Moreover, additional support for Claims 37, and 38 can be found on page 10 of the Specification, which states that:

> [T]he *E. cloacae* polypeptide is encoded by a nucleic acid of the invention contained in the Sequence Listing, or by a nucleic acid having at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% homology with a nucleic acid of the invention contained in the Sequence Listing.

One of ordinary skill in the art would have envisioned the scope of the invention to comprise SEQ ID NO:1394 and additional nucleic acid sequences that encode for SEQ ID NO:7056 that are based on the degeneracy of the genetic code. One of ordinary skill in the art would easily have identified multiple nucleic acid codons capable of encoding a given amino acid residue and, as a result, envision combinations of these codons to comprise numerous other nucleotide sequences encoding SEQ ID NO:7056. Thus, there is ample support for the claims as provided for by the Specification.

The Examiner states that

> [T]he specification does not teach what function the polypeptide has, or regions of the nucleic acid can be changed, or are conserved . . . . [A] nucleic acid claimed based upon the recited amino acid sequence would not be predictably detect *E. cloacae* specific . . . . No specific guidance has been provided in the instant specification and the person of skill in the art would not be able to make and use a nucleic acid to predictably detect *E. cloacae* which shares about 67% sequence identity with SEQ ID 1394, or a sequence of any size that shares 90 or 95% with SEQ ID NO:7056[.]

Prior to the filing of this patent application, functional domains for pseudouridine synthase (rsuA) in other species were well known in the art. As shown *supra,* the specification discloses that the nucleotide sequence represented by SEQ ID NO: 1394 encodes a polypeptide with a sequence identity to the polypeptide coded for by the rsuA gene. See Table 2 and the Sequence Listing as filed. For example, the PROSITE reference lists the functional domains for pseudouridine synthase. Because functional domains for the rsuA gene were well known in the art, one of ordinary skill in the art would have been able to envision and utilize isolated amino acids containing fragments with these functional domains having sequence identity to SEQ ID NO: 7056 at the time this application was filed. Moreover, these functional domains could be used in the screening of novel broad spectrum antibiotics across bacterial species.

Furthermore, Koonin teaches that pseudouridine synthases have certain signature motifs beyond the PROSITE motif. All three signature motifs taught by Koonin are found in the polypeptide SEQ ID NO:7056 encoded by SEQ ID NO:1394 as shown on page 11 of Applicants' Amendment and Reply of June 22, 2001. The teachings of Koonin present motifs identified with details which complement and expand on the PROSITE entries. Koonin also teaches that pseudouridine synthases perform essential functions. Since knowledge of the signature motifs are well known in the art, a person of ordinary skill in the art would be able to detect *E. cloacae* specific nucleic acid sequences.

Accordingly, Applicants respectfully submit that the Examiner erred in applying the rejection under 35 U.S.C. § 112, first paragraph. The invention as described in the Specification shows that the Applicants have possession of the claimed invention under 35 U.S.C. § 112.

Accordingly, Applicants respectfully request the appropriate withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

*3.* ***The rejection of Claims 5, 9, 29, and 50 under 35 U.S.C. § 102***

The Examiner has rejected claims 5, 9, 29, and 50 under 35 U.S.C. 102(b) as being anticipated by Blattner et al. ("Blattner") or Oshima et al. ("Oshima"). The Examiner states, in Office Action dated August 14th, 2002, page 7, that:

> [T]he sequence alignment of Blattner et al's sequence with the sequence of the instant Specification, with respect to a polynucleotide, SEQ ID NO: 1394, that encodes for the amino acid sequence of SEQ ID NO 7056, shows 94% over all sequence identity for the nucleic acid coding sequence.

Furthermore, the Examiner states:

> The amino acid sequence of Blattner shows two extensive stretches of identical amino acids, the first being a sequence of 25 sequential or consecutive amino acids that would be encoded by 75 nucleotides that would hybridize to the instantly claimed nucleic acid, and the second being a sequence of 52 sequential or consecutive amino acids that would be encoded by 156 nucleotides that would hybridize to the instantly claimed nucleic acid . . . .

Applicants submit that the Examiner is in error in applying the cited art. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *Connell v. Sears Roebuck & Co.*, 220 USPQ 193, 198 (Fed. Cir. 1983); *Verdegaal Bros. v. Union Oil Co. of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); MPEP § 2131.

The Examiner has not cited a prior art reference (*i.e.*, nucleic acid) that anticipates Applicants' claimed invention. "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Fiers v. Revel*, 984 F.2d 1164, 1170. Under *Fiers*, possession of the complete nucleic acid sequence must be in the prior art to anticipate a claimed nucleic acid sequence. Case law clearly shows that an amino acid sequence cannot be used to anticipate a nucleic acid sequence. Further, it is incorrect and improper to apply fully

degenerate probes from an amino acid sequence to screen a genomic DNA library. The Examiner must first have possession of a nucleic acid sequence before citing the nucleic acid sequence against the Applicants. As a result, the 25 or 52 consecutive amino acids cited in Blattner cannot anticipate 75 or 156 consecutive nucleic acids without possession of the DNA sequence itself.

Regarding claim 29, the Examiner cited a nucleotide sequence after reverse blasting SEQ ID NO:7056 (an amino acid sequence) against a nucleotide database. The reverse BLAST program returned a nucleic acid sequence that encoded an entirely-different protein from SEQ ID NO:7056. The cited nucleic acid sequence was NOT an EXACT match to the claimed nucleic acid sequence. A reference cited under 35 U.S.C. Section 102 must anticipate each and every element of a claim. As a result, the Examiner cannot apply that nucleic acid sequence against Applicants' claimed nucleic acid sequences because the sequence identity between the cited sequence and the claimed sequence is not 100% identical. Thus, the references cited by the Examiner cannot anticipate the invention of claim 29.

Regarding claims 5, 9, and 50, the Sequence Alignments, as shown in Exhibit 6, for the nucleic acid show no more than 23 consecutive nucleotides of SEQ ID NO:1394. Neither Blattner nor Oshima teaches or suggests 25 or 30 consecutive nucleotides of SEQ ID NO:1394. Thus, the cited references cannot anticipate the claimed invention of claims 5, 9, and 50.

Accordingly, Applicants respectfully submit that the invention as described in the specification shows that the Applicants' invention is distinguishable from that of Blattner or Oshima and respectfully request the withdrawal of the rejection under 35 U.S.C. § 102(b).

## X. CONCLUSION

For the foregoing reasons, it is submitted that the Examiner's rejections of claims 1-10, 29-41, 43-45, and 47-50 were erroneous, and reversal of her decisions is respectfully requested.

Respectfully submitted,

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APPENDIX A

**The Appealed Claims**

1. (Twice Amended) An isolated nucleic acid encoding an *E. cloacae* polypeptide wherein the nucleic acid comprises SEQ ID NO: 1394, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

2. A recombinant expression vector comprising the nucleic acid of claim 1 operably linked to a transcription regulatory element.

3. A cell comprising a recombinant expression vector of claim 2.

4. A method for producing an *E. cloacae* polypeptide comprising culturing a cell of claim 3 under conditions that permit expression of the polypeptide.

5. (Twice Amended) An isolated nucleic acid encoding an *E. cloacae* polypeptide or a fragment thereof, wherein the nucleic acid comprises at least 25 sequential bases of SEQ ID NO: 1394, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

6. A recombinant expression vector comprising the nucleic acid of claim 5 operably linked to a transcription regulatory element.

7. A cell comprising a recombinant expression vector of claim 6.

8. A method for producing an *E. cloacae* polypeptide comprising culturing a cell of claim 7 under conditions that permit expression of the polypeptide.

9. (Twice Amended) A probe comprising a nucleotide sequence including at least 25 sequential nucleotides of SEQ ID NO: 1394, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

10. (Thrice Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 30 consecutive nucleotides in length, wherein the sequence can hybridize under conditions of high stringency to a nucleic acid comprising SEQ ID NO: 1394, wherein said nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

29. An isolated nucleic acid encoding a polypeptide which comprises SEQ ID NO: 7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

30. A recombinant expression vector comprising the nucleic acid of claim 29 operably linked to a transcription regulatory element.

31. A cell comprising the recombinant expression vector of claim 30.

32. A method for producing an *E. cloacae* polypeptide comprising culturing the cell of claim 31 under conditions that permit expression of the polypeptide.

33. An isolated nucleic acid which encodes a polypeptide of E. *cloacae* consisting of a range of residues which is 3 - 222, 6-222, or 13 - 222 of SEQ ID NO: 7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

34. A recombinant expression vector comprising the nucleic acid of claim 33 operably linked to a transcription regulatory element.

35. A cell comprising the recombinant expression vector of claim 33, wherein the cell expresses the polypeptide encoded by SEQ ID NO: 1394.

36. A method for producing an *E. cloacae* polypeptide comprising culturing the cell of claim 33 under conditions that permit expression of the polypeptide encoded by SEQ ID NO: 1394.

37. An isolated nucleic acid encoding a polypeptide which comprises at least 90% sequence identity with SEQ ID NO: 7056, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

38. The isolated nucleic acid of claim 37, wherein the polypeptide comprises at least 95% sequence identity with SEQ ID NO: 7056.

39. A recombinant expression vector comprising the nucleic acid of claim 37 operably linked to a transcription regulatory element.

40. A cell comprising the recombinant expression vector of claim 37.

41. A method for producing an *E. cloacae* polypeptide comprising culturing the cell of claim 40 under conditions that permit expression of the polypeptide.

43. A recombinant expression vector comprising the nucleic acid of claim 42, operably linked to a transcription regulatory element.

44. A cell comprising the recombinant expression vector of claim 43, wherein the cell expresses the polypeptide encoded by SEQ ID NO: 1394.

45. A method for producing an *E. cloacae* polypeptide comprising culturing the cell of claim 44 under conditions that permit expression of the polypeptide encoded by SEQ ID NO: 1394.

47. A recombinant expression vector comprising the nucleic acid of claim 46, operably linked to a transcription regulatory element.

48. A cell comprising the recombinant expression vector of claim 47, wherein the cell expresses the polypeptide encoded by nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO: 1394.

49. A method for producing an *E. cloacae* polypeptide comprising culturing the cell of claim 48 under conditions that permit expression of the polypeptide encoded by nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO: 1394.

50. A probe comprising a nucleotide sequence including at least 30 sequential nucleotides of SEQ ID NO: 1394, wherein the isolated nucleic acid is not immediately contiguous with both of the coding sequences with which SEQ ID NO: 1394 is immediately contiguous in the naturally-occurring *E. cloacae* genome.